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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,396	10/28/2003	Nobuhiko Ozaki	61352-054	9206

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EXAMINER	
BOWERS, NATHAN ANDREW	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/694,396	OZAKI ET AL.
	Examiner	Art Unit
	Nathan A. Bowers	1744

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1-3, 5-8 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hollis (US 5846708) in view of Vogel (US 6758961) and Mikos (US 20030152548).

With respect to claims 1-3, Hollis discloses an integrated electrode comprising a substrate (Figure 15:212) equipped with at least one electrode conductor (Figure 15:220) and a wiring part that leads an electrical signal out from the electric conductor. A dielectric material (Figure 15:216) is coated over at least a part of the surface of the electric conductor. The integrated electrode can detect an electrical signal resulting from an electrophysiological change of a cell immobilized on the surface of the electric conductor, and the cell is an isolated cell or a cultured cell. This is described in Figure 15 and in column 8, line 59 to column 9, line 31. Hollis discloses an additional embodiment set forth in column 7, line 60 to column 8, line 28 and Figure 14 in which a silicon nitride dielectric layer (Figure 14:21C) and a dielectric gap (Figure 14:60) are positioned over a metal electrode (Figure 14:20C). This embodiment is also capable of detecting electrical signals resulting from electrophysiological changes of cells immobilized on the surface of the electric conductor. Hollis, however, does not expressly disclose in either embodiment that the dielectric material is a positively charged polymer.

Vogel discloses a device for measuring electrical properties of cells. The device includes a substrate (Figure 1:5) comprising an aperture (Figure 1:3) at which a biological analyte, such as a cell, is placed. Electrodes are positioned above and below the aperture in order to determine how the presence of the cell at the aperture affects the voltage difference across the substrate. This is described in column 6, line 53 to column 7, line 26. Column 3, lines 17-20 and column 3, line 63 to column 4, line 27 state that the aperture is provided with a positively charged material

that facilitates the attachment of the cell membrane. Vogel specifically discloses the use of polylysine and polyethyleneimine materials.

Hollis and Vogel are analogous art because they are from the same field of endeavor regarding microfluidic devices that are used to electrically monitor cells.

At the time of the invention, it would have been obvious to utilize polylysine and polyethyleneimine materials in the construction of the dielectric layer disclosed by Hollis. This is due to the fact that Vogel teaches that polylysine and polyethyleneimine provide good electrical attraction to cells, and thereby effectively aid in the detection of biological analytes. This would allow cells to move to the detection region of Hollis's device based on electrostatic interactions that would not damage the cell membrane. By promoting electrically tight binding, polylysine and polyethyleneimine materials would allow for detection to be conducted with greater sensitivity.

The combination of Hollis and Vogel still differs from Applicant's claimed invention because the references do not indicate that the dielectric material comprises a biguanide group.

Mikos discloses a polymer hydrogel that is modified to promote the immobilization of microorganisms. Paragraphs [0029] and [0032] state that guanide groups are used to accomplished increased cell adhesion. Paragraph [0035] specifically teaches that allylbiguanide-co-allylamine (PAB) is used in the construction of the hydrogel.

At the time of the invention, it would have been obvious to incorporate allylbiguanide-co-allylamine polymers in the dielectric material of Hollis and Vogel. Mikos teaches that allylbiguanide-co-allylamine materials are useful in facilitating the immobilization of cells upon

a polymer surface. By increasing the likelihood of effective cell immobilization, one would have been able to more accurately detect and electrically analyze microorganisms in a sample solution.

With respect to claim 5, Hollis, Vogel and Mikos disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. In addition, Hollis indicates in column 9, lines 18-20 that the electrodes are made from tungsten. Column 11, lines 25-41 further disclose the use of platinum, gold and tungsten electrodes.

With respect to claims 6 and 7, Hollis, Vogel and Mikos disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. Hollis additionally states that at least part of the electrode conductor coated with dielectric material is further coated with a cell adhesive protein immobilization material (Figure 14:22C). This is described in column 1, lines 18-29, column 10, lines 59-67 and column 18, lines 47-49.

With respect to claim 8, Hollis, Vogel and Mikos disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. Although Hollis does not expressly disclose specific capacitances, it is believed that Hollis's apparatus is fully capable of demonstrating a capacitance of 27 $\mu F/cm^2$ or greater at the applied voltage of 0 V. This is due to the fact that Hollis discloses identical electrode materials (platinum, gold and tungsten) as Applicant. In any event, it is believed that the creation of a specific desired capacitance of result effective variable that can be optimized through routine experimentation. One of ordinary skill in the art would be

motivated to ensure that a capacitance of 27 $\mu F/cm^2$ or greater is achieved if it was determined that this provided the results during experimentation. See MPEP 2144.05.

With respect to claims 12-14, Hollis, Vogel and Mikos disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. Hollis further teaches that the overall system includes a plurality of solution retaining parts (Figure 4:18, Figure 14:18C, Figure 15:224) that each include at least one surface of one of the electric conductors. Each solution retaining part disclosed in Figures 14 and 15 includes one electrical conductor. Each solution retaining part disclosed in Figure 4 includes multiple electrical conductors.

2) Claims 1-3 and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schoeniger (US 20030211637) in view of Vogel (US 6758961) and Mikos (US 20030152548).

With respect to claims 1-3, Schoeniger discloses an integrated electrode comprising a substrate (Figure 1:11) equipped with at least one electric conductor (Figure 1:13) and a wiring part which leads an electrical signal out from the electric conductor. This is disclosed in paragraphs [0033] and [0039]-[0041]. The integrated electrode can detect an electrical signal resulting from an electrophysiological change of an isolated cell (Figure 1:19) immobilized on the surface of the electric conductor. At least part of the surface of the electric conductor is coated with a silicon nitride dielectric material (Figure 1:14). Schoeniger, however, does not expressly disclose that the dielectric material is a positively charged polymer.

Vogel discloses a device for measuring electrical properties of cells. The device includes a substrate (Figure 1:5) comprising an aperture (Figure 1:3) at which a biological analyte, such as

a cell, is placed. Electrodes are positioned above and below the aperture in order to determine how the presence of the cell at the aperture affects the voltage difference across the substrate. This is described in column 6, line 53 to column 7, line 26. Column 3, lines 17-20 and column 3, line 63 to column 4, line 27 state that the aperture is provided with a positively charged material that facilitates the attachment of the cell membrane. Vogel specifically discloses the use of polylysine and polyethyleneimine materials.

Schoeniger and Vogel are analogous art because they are from the same field of endeavor regarding microfluidic devices that are used to electrically monitor cells.

At the time of the invention, it would have been obvious to utilize polylysine and polyethyleneimine materials in the construction of the dielectric layer disclosed by Schoeniger. This is due to the fact that Vogel teaches that polylysine and polyethyleneimine provide good electrical attraction to cells, and thereby effectively aid in the detection of biological analytes. This would allow cells to move to the detection region of Schoeniger's device based on electrostatic interactions that would not damage the cell membrane. By promoting electrically tight binding, polylysine and polyethyleneimine materials would allow for detection to be conducted with greater sensitivity.

The combination of Schoeniger and Vogel still differs from Applicant's claimed invention because the references do not indicate that the dielectric material comprises a biguanide group.

Mikos discloses a polymer hydrogel that is modified to promote the immobilization of microorganisms. Paragraphs [0029] and [0032] state that guanide groups are used to

accomplished increased cell adhesion. Paragraph [0035] specifically teaches that allylbiguanide-co-allylamine (PAB) is used in the construction of the hydrogel.

At the time of the invention, it would have been obvious to incorporate allylbiguanide-co-allylamine polymers in the dielectric material of Schoeniger and Vogel. Mikos teaches that allylbiguanide-co-allylamine materials are useful in facilitating the immobilization of cells upon a polymer surface. By increasing the likelihood of effective cell immobilization, one would have been able to more accurately detect and electrically analyze microorganisms in a sample solution.

With respect to claim 5, Schoeniger, Vogel and Mikos disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. In addition, Schoeniger teaches in paragraph [0039] that the electrode is made from platinum.

With respect to claims 6 and 7, Schoeniger, Vogel and Mikos disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. Schoeniger additionally states that the surface of the electric conductor coated with dielectric material is further coated with an immobilization material (Figure 1:17). The use of cell adhesive antibodies and peptides is expressed in paragraphs [0019] and [0032].

With respect to claim 8, Schoeniger, Vogel and Mikos disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. Although Schoeniger does not expressly disclose specific capacitances, it is believed that Schoeniger's apparatus is fully

capable of demonstrating a capacitance of 27 $\mu F/cm^2$ or greater at the applied voltage of 0 V. This is due to the fact that Schoeniger discloses identical electrode materials (platinum) as Applicant. In any event, it is believed that the creation of a specific desired capacitance of result effective variable that can be optimized through routine experimentation. One of ordinary skill in the art would be motivated to ensure that a capacitance of 27 $\mu F/cm^2$ or greater is achieved if it was determined that this provided the results during experimentation. See MPEP 2144.05.

3) Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Hollis (US 5846708) or Schoeniger (US 20030211637) in view of Vogel (US 6758961) and Mikos (US 20030152548) each as applied to claim 1, and further in view of Nisch (US 6315940).

The combination of Hollis, Vogel and Mikos and the combination of Schoeniger, Vogel and Mikos each disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejections above. The references, however, do not expressly disclose that the electric conductor is formed within at least one through-hole formed to the substrate.

Nisch discloses a microelectrode device for the investigation of biological cells. Nisch discloses a substrate (Figure 1:16) equipped with at least one electric conductor (Figure 1:21) capable of detecting an electrical signal resulting fro an electrophysiological change of a cell immobilized on its surface. The substrate includes a plurality of detection regions, as indicated in Figure 4, each comprising a through-hole (Figure 1:22) formed in the substrate.

Hollis, Schoeniger, Vogel, Mikos and Nisch are analogous art because they are from the same field of endeavor regarding microfluidic devices that are used to electrically monitor cells.

At the time of the invention, it would have been obvious to provide the electrical conductors disclosed by Hollis and Schoeniger at a plurality of through-holes. In column 3, lines 16-18, column 4, lines 1-24 and column 7, lines 16-28, Nisch teaches that this configuration is beneficial because it allows one to move cells to the electrode in a controlled manner using a mechanical means such as a vacuum. In this way, one is able to guarantee that the cells are correctly positioned during electrical testing.

4) Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schoeniger (US 20030211637) in view of Vogel (US 6758961) and Mikos (US 20030152548) as applied to claim 1, and further in view of Wolf (US 6376233).

Schoeniger, Vogel and Mikos disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above, however do not disclose that the integrated electrode is part of a system that includes a solution retaining part.

Wolf discloses an apparatus and method for recording electrophysiological activity of biological cells. A plurality of sensors (Figure 4:7) are provided to correspond with the wells (Figure 3:10) formed by a microtiter plate (Figure 3:11). This is described in column 6, lines 17-30 and in Figures 3-6. Each sensor array (Figure 4:7a) includes at least one stimulus electrode capable of interacting with cells. Wolf additionally discloses a retaining part (Figure 3) capable of culturing cells in a region directly above the sensor array.

Schoeniger, Vogel, Mikos and Wolf are analogous art because they are from the same field of endeavor regarding microfluidic devices that are used to electrically monitor cells.

At the time of the invention, it would have been obvious to provide the device proposed by Schoeniger with a solution retaining part capable of culturing cells. This would have been beneficial because it would have allowed one to encourage cell growth at the integrated electrode, thus removing the need to transport the cell sample from a remote location to the sensor. By eliminating this transportation step, one would be able to increase efficiency and reduce contamination and fluid loss.

Allowable Subject Matter

The indicated allowability of claim 1 is regrettably withdrawn in view of the newly discovered reference to Mikos (US 20030152548). Rejections based on the newly cited reference have been presented above.

Response to Arguments

In response to Applicant's amendment, all previously made rejections under 35 U.S.C. 112 in the prior Office Action (12/12/06) have been withdrawn.

Applicant's arguments filed 12 March 2007 with respect to the 35 U.S.C. 103 rejections pertaining to the combination of Hollis with Vogel have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground of rejection is made in view of the combination of Hollis and Vogel with Mikos.

Mikos addresses the deficiencies of Hollis and Vogel by teaching that allylbiguanide-co-allylamine materials are useful in facilitating the immobilization of cells upon a polymer surface.

By increasing the likelihood of effective cell immobilization, one would have been able to more accurately detect and electrically analyze microorganisms in a sample solution.

Applicant's arguments filed 12 March 2007 with respect to the 35 U.S.C. 103 rejections pertaining to the combination of Schoeniger with Vogel have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground of rejection is made in view of the combination of Schoeniger and Vogel with Mikos.

Mikos addresses the deficiencies of Schoeniger and Vogel by teaching that allylbiguanide-co-allylamine materials are useful in facilitating the immobilization of cells upon a polymer surface. By increasing the likelihood of effective cell immobilization, one would have been able to more accurately detect and electrically analyze microorganisms in a sample solution.

Conclusion

This is a non-final rejection.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan A. Bowers whose telephone number is (571) 272-8613. The examiner can normally be reached on Monday-Friday 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gladys Corcoran can be reached on (571) 272-1214. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NAB

GLADYS JP CORCORAN
SUPERVISORY PATENT EXAMINER